IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

DALE AARON, Personal Representative of the Estate of Randy Aaron, Plaintiff, v. WYETH, Defendant.	Civil Action No. 07-927 Judge David S. Cercone

MEMORANDUM IN SUPPORT OF DEFENDANT WYETH'S MOTION FOR SUMMARY JUDGMENT

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I. INTRODUCTION

In July 2005, 36-year-old Randy Aaron suffered from four mental health disorders: Major Depressive Disorder (or "MDD"), Generalized Anxiety Disorder, Panic Disorder, and Delusional Disorder. On July 27, 2005, a family practitioner, Dr. Jason Rasefske, prescribed the antidepressant Effexor for Aaron without seeing or speaking to either Aaron or the psychologist who had evaluated Aaron earlier that day. Dr. Rasefske scheduled no appointment to follow up with Randy Aaron. And Dr. Rasefske never spoke with Randy Aaron before Aaron committed suicide eleven days later, on August 7, 2005.

At the time Dr. Rasefske prescribed Effexor for Randy Aaron, the warnings about suicide contained in Effexor's labeling spanned more than two pages. Among other things, the labeling warned in bold type: "**Adults with MDD . . . being treated with antidepressants should be observed [closely] for clinical worsening and suicidality, especially during the initial few months of drug therapy**." The FDA had mandated these specific suicide-related warnings not only for Effexor, but for all modern antidepressants, starting in January 2005 – six months before Aaron's death – and the FDA had required similar suicide-related warnings since April 2004.

In this action, plaintiff pleads that it was not Randy Aaron's underlying mental health disorders, but rather inadequate warnings on his antidepressant medication, that caused him to commit suicide. Plaintiff asserts negligent failure-to-warn, negligent design, and express warranty claims against Wyeth, Effexor's manufacturer. Plaintiff's warning claim fails under the learned intermediary doctrine for two reasons. First, plaintiff must establish that Effexor's warnings were inadequate. Yet Effexor's detailed suicide-related warnings were adequate as a matter of law and, in any event, Dr. Rasefske was aware of the suicide-related risks that depressed patients like Randy Aaron faced. Second, the learned intermediary doctrine requires plaintiff to establish that different warnings would have (1) prevented Dr. Rasefske from

prescribing Effexor for Randy Aaron, and (2) averted Randy Aaron's suicide. On these facts – where the prescribing physician never met or spoke to the patient – plaintiff cannot make either showing.

Separately, federal law preempts plaintiff's warning claim because there is "clear evidence that the FDA would not have approved a change to" Effexor's suicide-related warnings. *Wyeth v. Levine*, 129 S. Ct. 1187, 1198 (2009). For years, the FDA has monitored (and even developed) the science relating to antidepressants and suicidality, and the FDA always required that antidepressants' suicide-related warnings conform to the FDA's own scientific judgments. Plaintiff's claim that Pennsylvania law required additional suicide-related warnings in July 2005 conflicts with the FDA's regulatory judgment that only its warnings should be provided.

Finally, plaintiff's negligent design and express warranty claims are makeweights that fail because plaintiff cannot produce summary judgment evidence to establish required elements of those claims; namely, that (1) there was an alternative, feasible, safer design for Effexor, and (2) Wyeth somehow expressly warranted that depressed patients taking Effexor would not commit suicide. The Court should enter summary judgment in favor of Wyeth.[1]

II. ARGUMENT

A. The Learned Intermediary Doctrine Bars Plaintiff's Failure-To-Warn Claim.

Under Pennsylvania's learned intermediary doctrine, "when a drug 'is available only upon prescription of a duly licensed physician, the warning required is not to the general public or to the patient, but to the prescribing doctor.'" *Coyle v. Richardson-Merrell, Inc.*, 526 Pa. 208,

[1] Under Rule 56(c), summary judgment "should be rendered if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." "When the moving party has carried its burden under Rule 56(c), its opponent must do more than simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986) (citations and footnote omitted). "Where the record taken as a whole could not lead a rational trier of fact to find for the nonmoving party, there is no 'genuine issue for trial.'" *Id.* (citation omitted).

213, 584 A.2d 1383, 1385 (1991) (quoting *Incollingo v. Ewing*, 444 Pa. 263, 288, 282 A.2d 206, 220 (1971)). "At bottom it is the physician who is required to make the individualized medical judgment of what treatment to administer in a given instance, and it is the physician who is ultimately held accountable for that decision." *Mazur v. Merck & Co.*, 964 F.2d 1348, 1358 (3d Cir. 1992) (applying Pennsylvania law) (footnote omitted).

The learned intermediary doctrine bars plaintiff's negligent failure-to-warn claim for two reasons. First, plaintiff cannot establish that Effexor's suicide-related warnings were inadequate in July 2005. Second, plaintiff cannot establish proximate causation because there is no evidence that different warnings would have either changed Dr. Rasefske's decision to prescribe Effexor or prevented Randy Aaron's suicide.

1. Plaintiff cannot establish that Effexor's warnings were inadequate.

"Under Pennsylvania law the determination whether a warning is adequate is a question of law." *Mazur*, 964 F.2d at 1366 (citation omitted); *accord Demmler v. SmithKline Beecham Corp.*, 448 Pa. Super. 425, 431, 671 A.2d 1151, 1154 (1996). A prescription drug manufacturer "'is liable only if [it] fails to exercise reasonable care to inform [the physician] of the facts which make [the drug] likely to be dangerous.'" *Mazur*, 964 F.2d at 1354-55 (Third Circuit's italics omitted) (quoting *Baldino v. Castagna*, 505 Pa. 239, 244, 478 A.2d 807, 810 (1984), which cited *Incollingo*, 444 Pa. at 288 n.8, 282 A.2d at 220 n.8, and *Restatement (Second) of Torts* § 388). "Adequacy of warnings is determined on the basis of information that was known or knowable at the time the cause of action accrued. Warnings that meet federal drug labeling requirements are afforded some deference." *Mazur*, 964 F.2d at 1366 (citations omitted).

Here, plaintiff cannot establish a genuine issue relating to the adequacy of Effexor's suicide-related warnings for two reasons: (1) Effexor's labeling included detailed suicide-related

warnings that were adequate as a matter of law; and (2) the prescribing physician, Dr. Rasefske, was aware of the relevant risks.

a. Effexor's warnings were adequate.

When Dr. Rasefske prescribed Effexor for Randy Aaron in July 2005, Effexor's labeling contained more than two pages of suicide-related warnings that the FDA had crafted and required for the entire class of modern antidepressants just six months earlier, in January 2005. (Concise Statement of Undisputed and Material Facts in Support of Defendant Wyeth's Motion for Summary Judgment ("SUMF")[2] ¶ 56.) The cover page had a "black box" warning entitled "**Suicidality in Children and Adolescents**."[3] (SUMF ¶ 58 (bold in original).) The "Warnings" section began with an FDA-crafted caption – "**Clinical Worsening and Suicide Risk**" – followed by nearly two pages of FDA-crafted single-spaced text. (SUMF ¶ 57 (bold in original).)[4] That text told physicians that "adult" patients who, as Randy Aaron did, suffered from Major Depressive Disorder (or "MDD"), "may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs." (*Id*.) The warning also advised that "**[a]dults**" who suffered, as Randy Aaron did, from "**MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed . . . for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases**." (*Id.* (bold in original).)

[2] All subsequent references to SUMF ¶ __, shall be to the Concise Statement of Undisputed and Material Facts in Support of Defendant Wyeth's Motion for Summary Judgment, which is being filed contemporaneously herewith.

[3] "Black box" warnings address "[s]pecial problems, particularly those that may lead to death or serious injury." 21 C.F.R. § 201.57(e) (Apr. 21, 2006).

[4] This warning is reproduced in full in the Statement of Undisputed and Material Facts at ¶ 57.

The warning then listed eleven symptoms that had "been reported in adult . . . patients being treated with antidepressants" and warned that, "[a]lthough a causal link . . . ha[d] not been established, there [wa]s concern that such symptoms may represent precursors to emerging suicidality." (*Id.*) The warning recommended that physicians consider changing drugs "in patients . . . who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality." (*Id.*) Finally, the warning said that "**[f]amilies and caregivers of pediatric patients being treated with antidepressants . . . should be alerted about the need to monitor patients for the emergence of . . . suicidality,**" including "**daily observation**," and warned that "[f]amilies and caregivers of adults being treated for depression should be similarly advised." (*Id.* (bold in original)).

Later scientific developments have only confirmed the adequacy of Effexor's suicide-related warnings as of July 2005 for adults like Randy Aaron.[5] In November 2006, after analyzing data from all modern antidepressant manufacturers' adult clinical trials (the "FDA Adult Analysis"), the FDA's researchers concluded that the data did not show an increased risk of suicidality in adults over age 24 – the age group that included Randy Aaron. (SUMF ¶ 61.) Instead, their analysis suggested *decreased risks* for 36-year-old depressed patients for the two primary outcomes being measured – suicidality and suicidal behavior.[6] (Clinical Review: Relationship Between Antidepressant Drugs and Suicidality In Adults at 28 (Table 17), 30 (Table 18) (Nov. 17, 2006) (SUMF Appx. Tab 26).) Thus, later scientific evidence confirms the

[5] Of course, the "[a]dequacy of warnings is determined on the basis of information that was known or knowable at the time the cause of action accrued." *Mazur*, 964 F.2d at 1366 (citations omitted). But, if there were any doubt about the adequacy of Effexor's warnings, later scientific and regulatory developments would remove it, because those developments show no increased risk of suicidality for patients in Randy Aaron's age group.

[6] With two exceptions where the results were statistically significant (*i.e.*, for suicidality in the 25-44 and 25-64 age groups), these results were statistically insignificant and, for that reason, do not establish a decreased risk. But the important point here is that, after examining clinical trial data from all antidepressant manufacturers for 372 clinical trials involving nearly 100,000 patients, there was no statistically significant *increased risk*. Therefore, the current science does not support additional suicide-related warnings in this age group.

adequacy of the FDA's warnings that were in effect in July 2005 for 36-year-old adults like Randy Aaron.

Where prescription drug warnings advise physicians of the specific risk at issue, courts enter summary judgment under the learned intermediary doctrine for lack of a genuine issue as to the adequacy of the warnings.[7] *Demmler*, 448 Pa. Super. at 433, 671 A.2d at 1155; *see also Moore v. Watson Pharms. Labs*, No. 01-4260, 2002 U.S. Dist. LEXIS 636, *7 (E.D. Pa. Jan. 15, 2002) (granting motion to dismiss failure-to-warn claim relating to prescription drug where "the reactions of which plaintiff complains [we]re duly noted in the [Physicians' Desk Reference]"). That result should apply here.

b. Dr. Rasefske was aware of the relevant risks.

"[I]t is the duty of the prescribing physician to be fully aware of . . . the characteristics of the drug he is prescribing," as well as to "'use his independent medical judgment, taking into account the data supplied to him by the manufacturer, *other medical literature, and any other source available to him*, and weighing that knowledge against the personal medical history of [the] patient, whether to prescribe a given drug.'" *Coyle*, 526 Pa. at 213-14, 584 A.2d at 1385-86 (italics added) (citations omitted). "[T]he information supplied by the drug manufacturer is only one source a physician must consult . . . in determining whether a given drug is appropriate for a particular patient." *Brecher v. Cutler*, 396 Pa. Super. 211, 218, 578 A.2d 481, 495 (1990). Thus,

[7] "Generally, expert medical testimony is required to determine whether the drug manufacturer's warning to the medical community [wa]s adequate because prescription drugs are likely to be complex medicines, esoteric in formula and varied in effect." *Demmler*, 448 Pa. Super. at 432, 671 A.2d at 1154 (citation omitted). Here, plaintiff disclosed an unsworn expert report from Dr. Joseph Glenmullen, a practicing psychiatrist, who criticized Effexor's suicide-related warnings on various grounds. Dr. Glenmullen's opinions, several of which are inadmissible under Rule 702 and *Daubert*, do not establish the inadequacy of Wyeth's warnings. But where, as here, "[t]he substance of this report was not sworn to by the alleged expert," "the purported expert's report is not competent to be considered on a motion for summary judgment." *Fowle v. C & C Cola*, 868 F.2d 59, 67 (3d Cir. 1989) (citing *Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 158 n.17 (1970)); *accord Hickenbottom v. Nassan*, No. 03-223, 2007 U.S. Dist. LEXIS 24336, *12 (W.D. Pa. Mar. 30, 2007) (Conti, J.) (refusing to consider multiple unsworn expert statements in connection with summary judgment motion). Considering Dr. Glenmullen's unsworn report would be particularly inappropriate here because, despite multiple requests, plaintiff did not produce him for deposition.

a prescriber may be adequately warned even if his knowledge came from a source other than the drug's labeling.

Here, Dr. Rasefske testified that, as of July 2005, he recalled Effexor's suicide-related warnings addressing only pediatric and adolescent patients and not adult patients like Randy Aaron. (SUMF ¶ 26.). In this respect, his recollection was incorrect in that, as explained at pages 4-5 above, Effexor's suicide-related warnings repeatedly addressed adult patients.[8] But, even for defendant physicians who affirmatively disclaim knowledge, courts "decline to accept the proposition that a qualified doctor can … turn himself into a dupe." *Incollingo*, 444 Pa. at 284, 282 A.2d at 218. When the prescribing physician "could not remember the package inserts as of the date of his deposition," the physician nonetheless was warned so long as he or she "read the literature," particularly if the prescribing physician "has not asserted that he was not adequately warned." *Cahill v. Miles, Inc.*, No. 91-1966, 1992 U.S. Dist. LEXIS 7192, *6 (E.D. Pa. May 12, 1992).

Dr. Rasefske understandably had an imperfect recollection of the relevant suicide-related *warnings* at his deposition – a deposition taken over two-and-a-half years after (1) the Effexor prescription at issue here and (2) Dr. Rasefske stopped seeing patients.[9] But he had ample information about suicide-related *risks* facing depressed patients like Randy Aaron. Dr. Rasefske regularly treated depressed patients with modern antidepressants and, not surprisingly,

[8] Dr. Rasefske could not recall the exact version of Effexor's labeling that he had last reviewed before prescribing Effexor for Randy Aaron in July 2005, but his "best estimate" was that he had reviewed Effexor's labeling in "about [the prior] six months." (SUMF ¶ 26.) Other than the FDA's pediatric "black box" warning that was added in January 2005, the suicide-related warnings that were in Effexor's – and every other modern antidepressant's – "Clinical Worsening and Suicide Risk" warning in July 2005 had been there since June 2004 with only minor changes. (SUMF ¶ 53.) Any labeling for Effexor – or any other modern antidepressant – that Dr. Rasefske reviewed for over a year before he prescribed Effexor for Randy Aaron included a lengthy, detailed "Clinical Worsening and Suicide Risk" warning that repeatedly warned about potential risks to adults. (SUMF ¶¶ 26, 53.)

[9] In October 2005, Dr. Rasefske took a position as a physician disability specialist with the Commonwealth of Pennsylvania and no longer practices medicine. (SUMF ¶ 26.)

did his best to keep abreast of their risks and benefits. (SUMF ¶ 25.) In July 2005, Dr. Rasefske was aware that depressed patients are at substantial and serious risk of self-harm or suicide and that they may not be forthcoming in revealing suicidal plans. (SUMF ¶ 20.) He knew that depressed patients may have emerging suicidal ideation and behavior, whether or not they are taking antidepressants, that may persist until significant remission of the depression occurs. (SUMF ¶ 21.) Dr. Rasefske was aware that patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, as well as that worsening of depression or the emergence of suicidal impulses should prompt consideration of changing the therapeutic regime, including possibly discontinuing the medication. (SUMF ¶ 22.) And he knew that patients and their family should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, and other symptoms after beginning medication. (SUMF ¶ 23.)

Indeed, when Dr. Rasefske saw depressed patients, he "discussed [with the patients that] if the feelings of suicidality were to manifest, that [they] needed to contact [him], and when [he] saw patients [he] always tried to contract for safety . . . and make sure [he] at least ha[d] that discussion with them." (SUMF ¶ 24.) And by "contract for safety," he meant "asking [the patient] to agree to call [him] if they felt like they might harm themselves." (*Id.*)

Where the prescribing physician was aware of the relevant risks, courts routinely have entered summary judgment for prescription drug manufacturers because the prescribing physician was adequately warned. *Brecher v. Cutler*, 396 Pa. Super. 211, 221, 578 A.2d 481, 486 (1990) (affirming summary judgment for prescription drug manufacturer based on physician's knowledge); *Parkinson v. Guidant Corp.*, 315 F. Supp. 2d 741, 749 (W.D. Pa. 2004) (Diamond, J.) (entering summary judgment for medical device manufacturer where physician

was familiar with the relevant risks); *see also Leibowitz v. Ortho Pharm. Corp.*, 224 Pa. Super. 418, 432 n.3, 307 A.2d 449, 457 n.3 (1973) (affirming defense verdict on that basis). For example, the Fifth Circuit recently affirmed the entry of summary judgment in a case involving claims similar to those here because that prescribing physician "was aware of the risk for suicide, not just from reading the warning label for Effexor, which mentioned the risk for suicide twice, but also from his training and experience as a psychiatrist treating depressed patients." *Ackermann v. Wyeth Pharmaceuticals*, 526 F.3d 203, 212 (5th Cir. 2008) (applying Texas law). Whatever the state of Dr. Rasefske's recollection of Effexor's *warnings*, he was aware of the suicide-related *risks* that faced depressed patients taking antidepressants, including Randy Aaron.

2. Plaintiff cannot establish proximate causation.

"'In the duty to warn context, assuming that plaintiffs have established both duty and a failure to warn, plaintiffs must further establish proximate causation by showing that had defendant issued a proper warning to the learned intermediary, he would have altered his behavior and the injury would have been avoided.'" *Demmler*, 448 Pa. Super. at 434, 671 A.2d at 1155 (citation omitted). If a plaintiff "present[s] no evidence that a different warning would have changed [the particular prescribing physician's] decision to prescribe" the drug, the defendant is entitled to summary judgment because, in that event, the plaintiff has "failed to produce evidence essential to [the] cause of action." *Lineberger v. Wyeth*, 2006 PA Super 35, ¶ 24, 894 A.2d 141, 151 (2006).

If a prescribing physician "negligently prescrib[es]" a drug by disregarding the warnings, the physician's conduct is the "causal link between [the drug use] and the plaintiff's injuries," and "the learned intermediary doctrine places responsibility at the door of the prescribing physician and serves to shield the drug manufacturer." *Ferrara v. Berlex Labs., Inc.*, 732 F. Supp. 552, 555 (E.D. Pa.) (applying Pennsylvania law), *aff'd mem.*, 914 F.2d 242 (3d Cir. 1990).

"To create a jury question, the evidence introduced must be of sufficient weight to establish … some reasonable likelihood that an adequate warning would have prevented the plaintiff from receiving the drug." *Demmler*, 448 Pa. Super. at 434, 671 A.2d at 1155 (citation and internal quotation marks omitted).

Here, plaintiff cannot prove proximate causation for two reasons. First, Dr. Rasefske would not have altered his prescribing behavior even if Effexor's labeling had included different suicide-related warnings as of July 2005. It is undisputed that, on July 27, 2005, without ever seeing or speaking to Randy Aaron, Dr. Rasefske prescribed Aaron a one month's supply of Effexor with five refills. (SUMF ¶ 17-18.) Dr. Rasefske never discussed Randy Aaron with Joseph Perry, Ph.D., the psychologist who saw Randy Aaron three times just before the suicide. (SUMF ¶ 17.) On analogous facts, Senior Judge Jack Weinstein recently granted summary judgment based on Pennsylvania's learned intermediary doctrine because "[t]here [wa]s no evidence that a different warning regarding [the drug] would have changed [the prescribing physician's] decision to prescribe [the drug] to" the plaintiff. *Clark v. Eli Lilly & Co.*, No. 04-MD-1596, 2009 WL 1514427, *14 (E.D.N.Y. May 29, 2009).

Second, there is no evidence that different warnings would have prevented this suicide. The psychologist who met Randy Aaron, Dr. Perry, (1) asked Aaron repeatedly whether he had suicidal thoughts; and (2) told Aaron several times that he needed to see a psychiatrist, needed to be hospitalized, and should seek help if he had thoughts of self-harm or suicide. (SUMF ¶¶ 13-14, 28-30.) Yet Randy Aaron denied having suicidal thoughts, never saw a psychiatrist, refused hospitalization, and sought no help before committing suicide on August 7, 2005. (*Id.*) Nothing Wyeth said in Effexor's labeling would have changed that sequence. Plaintiff cannot establish

that any supposed inadequacy in Effexor's suicide-related warnings to Dr. Rasefske proximately caused Randy Aaron's suicide.

B. Plaintiff's Negligent Failure-To-Warn Claim Is Preempted.

1. *Wyeth v. Levine*

Earlier this year in *Wyeth v. Levine*, 129 S. Ct. 1187 (2009), the Supreme Court considered a claim that federal law preempted state-law, failure-to-warn claims relating to a prescription drug.[10] There, in April 2000, a physician's assistant attempted to inject an anti-nausea drug, Phenergan, into a vein in a patient's arm, but mistakenly injected it into her artery, where the drug is highly corrosive, ultimately resulting in amputation. The assistant used the IV-*push* method of administration that, unlike the slower IV-*drip* method, injects the drug quickly. The *Levine* plaintiff alleged that the drug manufacturer should have provided additional warnings directing physicians to use the slower (and therefore less risky) IV-drip method. The trial court denied the defendant's preemption-based summary judgment motion, a jury returned a verdict for the plaintiff, and the Vermont Supreme Court affirmed.

Because the FDA's regulation of warnings relating to the risk of intra-arterially injecting Phenergan was the central issue before it, the Court summarized the relevant regulatory history. The FDA approved Phenergan in 1955 and, although the relevant warnings were unchanged, the manufacturer proposed new Phenergan labeling in response to revised FDA labeling regulations

[10] Preemption based on the Supremacy Clause, U.S. Const. art. VI, cl. 2, may occur when (1) Congress expressly preempts state regulation; (2) Congress intends federal law to "occupy the field;" or (3) state law conflicts with federal law. *Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000). Only the last type of preemption – conflict preemption – is at issue here. Conflict preemption occurs "where it is impossible for a private party to comply with both state and federal law" or when "'under the circumstances of [a] particular case, [the challenged state law] stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Id.* at 372-73 (citation omitted). Preemption may apply to state-law tort obligations: "[C]ommon-law liability is 'premised on the existence of a legal duty,' and a tort judgment therefore establishes that the defendant has violated a state-law obligation. And while the common-law remedy is limited to damages, a liability award '"can be, indeed is designed to be, a potent method of governing conduct and controlling policy."'" *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1008 (2008) (citation omitted). Similarly, federal regulations "have no less pre-emptive effect than federal statutes." *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982).

in 1981. *Id.* The FDA did not respond, so the pre-1981 labeling remained in effect. *Id.* Six years later, in 1987, the FDA suggested that the drug manufacturer add different intra-arterial exposure warnings and, in 1988, it proposed revised warnings. *Id.* Again, the FDA did not act, so the pre-1981 labeling remained in effect. *Id.* Eight years later, in 1996, the FDA asked the defendant for the labeling then in use, which was the pre-1981 labeling, and, without addressing the still-pending 1988 proposed labeling with the revised intra-arterial injection warnings, "instructed [the manufacturer] to '[r]etain verbiage in current label' regarding intra-arterial injection." *Id.* at 1192. Seventeen years after the drug manufacturer submitted its 1981 proposed labeling – in 1998 – the FDA approved that labeling after approving changes that were unrelated to the intra-arterial injection warnings. *Id.*

The Court affirmed the Vermont state court judgment for the plaintiff. Initially, the Court addressed the claim that, because federal law requires using the FDA-approved labeling's exact language, it was impossible "to comply with both the state-law duties underlying [plaintiff's] claims and its federal labeling duties." *Id.* at 1196. The Court found that additional warnings could have been provided under the "change being effected" or "CBE" regulation, 21 C.F.R. § 314.70(c)(6)(iii),[11] which allows warnings changes without prior (but subject to later) FDA approval. Addressing the assertion that, under 21 C.F.R. § 314.3,[12] CBE warnings changes are permitted only when there is "newly acquired information," the Court said that new information

[11] The FDA substantially revised and, in some instances, renumbered its drug labeling regulations as of June 30, 2006. Because Effexor's labeling was prepared under the earlier versions of the FDA regulations, they are relevant here, and all citations to FDA regulations are to the earlier versions unless otherwise indicated.

[12] "[N]ewly acquired information" was defined in 21 C.F.R. § 314.3 and expressly required in 21 C.F.R. § 314.70(c)(6)(iii) as of August 22, 2008. But the "FDA . . . amend[ed] these provisions to *reaffirm* that a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information and to *clarify* that a CBE supplement may be used . . . only if there is sufficient evidence of a causal association with the drug." Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2,848, at 2,849 (Jan. 16, 2008) (italics added).

had accumulated from 1967 forward that "could have [been] analyzed . . . and [then] added [through] a stronger warning about IV-push administration of the drug." *Id.* at 1197.

Next, the Court characterized the defendant's argument as being "that the FDA, rather than the manufacturer, bears primary responsibility for the drug labeling," a view it rejected. *Id.* The Court noted, however, that, "[o]f course, the FDA retains authority to reject labeling changes made pursuant to the CBE regulation . . . , just as it retains such authority in reviewing all supplemental applications. But absent clear evidence that the FDA would not have approved a change to Phenergan's label, [the Court] w[ould] not conclude that it was impossible . . . to comply with both federal and state requirements." *Id.* at 1198. In the Court's view, the manufacturer "ha[d] offered no such evidence" because, among other things, "it [had not] supplied the FDA with an evaluation or analysis concerning the specific dangers posed by the IV-push method." *Id.* at 1198-1199.

Finally, *Levine* rejected the claim that the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, "establishes both a floor and a ceiling for drug regulation." *Id.* at 1199. The Court recognized that federal agencies "have a unique understanding of the statutes they administer and an attendant ability to make informed determinations about how state requirements may pose an 'obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Id.* at 1201. The Court declined, however, to defer to the FDA in this instance because (1) there was a "procedural failure" in that the FDA's statement about the preemptive effect of the FDCA was not in a regulation adopted after notice and comment rulemaking;[13] (2) the FDA had changed its view on this issue over time; and (3) the FDA "ha[d]

[13] The FDA stated this view in a regulatory preamble, rather than the actual text of the regulation. Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products (Part II), 71 Fed. Reg. 3,922, at 3,935 (Jan. 24, 2006) ("FDA interprets the act to establish both a 'floor' and a 'ceiling'"). Thus, there was no formal opportunity for notice and comment.

no special authority to pronounce on pre-emption absent delegation by Congress," which had not occurred here. *Id.* at 1201-03 (citation omitted). "Although [the Court] recognize[d] that some state-law claims might well frustrate the achievement of congressional objectives, this [wa]s not such a case." *Id.* at 1204.

2. The FDA Comprehensively Regulated Modern Antidepressants' Suicide-Related Warnings.

In *Levine*, the Court said "'the record show[ed] that the FDA ha[d] paid very little attention to the issues [relating to intra-arterial injection of Phenergan] raised by the parties at trial.'" 129 S. Ct. at 1203 n.14 (quoting the trial court with approval). For antidepressants, the history of the FDA's regulation of suicide-related warnings for Effexor and other modern antidepressants reflects extensive, ongoing, and careful FDA oversight and control.

a. 1987 to June 2003

Starting with the FDA's approval of the first modern antidepressant – Prozac – in 1987, the FDA required a suicide precaution on every modern antidepressant, including Effexor: "The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs," and "[c]lose supervision of high-risk patients should accompany initial drug therapy." (SUMF ¶ 33 (FDA Prepared Statement to H. of Rep. Subcomm.).) Through 2003, the FDA's judgment was that the scientific record did not show increased suicide-related risks for modern antidepressants. Thus, the FDA repeatedly rejected proposals to change this precaution because, in the agency's view, the underlying science did not support additional warnings. (SUMF ¶ 34.)

In early 1990, Dr. Martin Teicher reported that six patients taking Prozac had suicidal thoughts. (SUMF ¶ 35.) The Citizens Commission on Human Rights ("CCHR") then filed a citizen petition asking the FDA withdraw Prozac's approval based on, among other things, Dr.

Teicher's results. In July 1991, the FDA rejected CCHR's petition because "[t]he data and information . . . do not indicate that Prozac causes suicidality or violent behavior." (SUMF ¶ 36.)

In May 1991, Public Citizen Research Group ("Public Citizen") filed a citizen petition seeking to have the FDA require a "black box" warning relating to Prozac and suicidality. (SUMF ¶ 37.) In September 1991, the FDA convened a scientific advisory committee – its Psychopharmacological Drugs Advisory Committee ("PDAC") – to review the evidence regarding antidepressants and suicidality. (SUMF ¶ 38.) Witnesses raised concerns that additional warnings "would generally harm the patient community and make it more difficult to be treated with these life-saving medications." (*Id*.) An FDA director testified that "evaluation by FDA scientists, outside consultants, and by our physicians, have not led [the FDA] to conclude that there is a differential rate of risk for Prozac related to suicidal thoughts, acts, or other violent behaviors" and that "the net effect" of additional warnings "might be a reduction in the use of antidepressants . . . that . . . might cause overall injury to the public." (SUMF ¶ 39.) Ultimately, the FDA PDAC found no "credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or violent behaviors" and voted against a labeling change. (*Id.*) The FDA thus denied Public Citizen's citizen petition in June 1992. (*Id.*)

Other FDA PDAC meetings produced similar results. At the April 30, 1993, meeting relating to Effexor's initial approval, the FDA's Dr. Knudsen observed that the FDA had employed several strategies to explore a possible relationship between Effexor and suicidality, and none revealed a greater risk of suicidality for Effexor. (SUMF ¶ 40.) According to the FDA's Dr. Laughren, "subsequent to the Prozac experience, all subsequent NDAs [new drug

applications] for all antidepressants were looked at in the same way," and the FDA "never s[aw] a signal for excess suicidality." (SUMF ¶ 41.)

In January 1997, the FDA received yet a third citizen petition, this time asking the FDA to require warnings stating that people at risk for suicide should be carefully observed and consider taking a sedative when beginning Prozac therapy. The FDA denied this petition, stating that, while it had "continued to monitor carefully reports of a possible connection between Prozac and increased suicidality," "no credible scientific evidence ha[d] caused the agency to depart from its conclusion that the current Prozac labeling appropriately reflect[ed] the level of concern about Prozac and suicidality." (SUMF ¶ 42.)

In September 2002, the FDA filed an *amicus curiae* brief in a case involving claims that Pfizer's modern antidepressant, Zoloft, caused a 1998 suicide. (SUMF ¶ 43.) There, the FDA said that, "given the [FDA's] repeated negative determinations on the subject, had Pfizer given a warning as to a causal relation between Zoloft and suicide [in 1998], FDA would have disapproved that warning. Indeed, based on its current scientific knowledge, FDA would still do so *today* [in September 2002]." (*Id.* (italics added)). The FDA later submitted multiple *amicus curiae* briefs reaffirming this conclusion, including one in the United States District Court for the Eastern District of Pennsylvania, where the FDA stated that its "scientific judgment in October 2003 . . . was that there was no reasonable evidence available at that time of an association between adult use of the drug and suicide or suicidality. To include on a drug's label a warning about a drug's effects, when FDA has determined that such a warning is not based on reliable scientific evidence, would be 'false or misleading,' 21 U.S.C. § 352(a), (f), and would constitute unlawful misbranding." (SUMF ¶ 44.)

Consistent with its factual statements about its current (or recent) regulatory judgments in *amicus curiae* briefs, the FDA rejected suicide-related language that Wyeth proposed adding to Effexor's labeling in late 2002. (SUMF ¶ 45.) In Effexor's pediatric clinical trials that were completed in mid-2002, the Effexor-treated patients reported higher levels of hostility (2% versus <1%) and suicidal ideation (2% versus 0%) than placebo-treated patients. (*Id.*) In September 2002, Wyeth submitted proposed Effexor labeling to the FDA that reported this information, but the FDA rejected the proposed changes and, in March 2003, directed Wyeth to continue using the existing language. (*Id.*)

b. June 2003 and afterwards

Beginning in June 2003, there were scientific developments that, over time, caused the FDA to revise its scientific and regulatory judgments about modern antidepressants and suicidality. As the FDA's scientific views changed with the evolving science, the agency retained firm control over the suicide-related warnings required on the labeling of modern antidepressants.

The FDA announced in June 2003 that GlaxoSmithKline had reported "a possible increased risk of suicidal thinking and suicidal attempts" in pediatric clinical trials for its modern antidepressant Paxil. (SUMF ¶ 46.) On August 8, 2003, Wyeth added a CBE precaution to Effexor's labeling reporting that, "[i]n pediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorder [patients], suicide-related adverse events such as suicidal ideation and self-harm." (SUMF ¶ 47.) On March 19, 2004, the FDA *rejected* this CBE language because the FDA did "not believe that a causal association between children taking [Effexor] and the emergence of suicidality has as yet been definitively established" and, thus, did "not agree with the labeling changes proposed in [Wyeth's] August 8, 2003 [CBE] submission." (SUMF ¶ 48.) In May 2004, after Wyeth tried to address the FDA's concerns by

proposing revised language, the FDA again told Wyeth to remove this information because "the [FDA's] currently proposed language for **WARNINGS** is intended to comprehensively address this complex issue and [the FDA's] current understanding of the available data, and we feel it would be confusing and potentially misleading to maintain [Wyeth's] proposed language." (SUMF ¶ 49.)

The FDA did not stand still. Shortly after the June 2003 announcement about Paxil's pediatric clinical trial data, the FDA required all antidepressant manufacturers to submit their pediatric clinical trial data so that FDA-commissioned researchers at Columbia University could perform a meta-analysis,[14] an analysis no single manufacturer could perform because only the FDA had the power to compel all manufacturers to provide their proprietary data. (SUMF ¶ 50.) The FDA also issued a Public Health Advisory on October 27, 2003, advising physicians of its then-ongoing analysis of pediatric clinical trial data and addressing "press and medical journal reports of suicide attempts and completed suicides in pediatric patients receiving antidepressants." (SUMF ¶ 51.)

In February 2004, the FDA's PDAC met to consider initial analyses of the pediatric clinical trial data and "advised the FDA to inform the public and health care workers . . . of the level of concern regarding possible harm to a minority of children on antidepressants and the signs associated with the side effects." (SUMF ¶ 52.) Based on this recommendation, the FDA issued a March 22, 2004 Public Health Advisory announcing new, class-wide suicide warnings for modern antidepressants to go into effect in April 2004. (SUMF ¶ 53.) The April 2004 warnings included a version of the "**Clinical Worsening and Suicide Risk**" warning that

[14] "Meta-analysis is a method of pooling study results to arrive at a single figure to represent the totality of the studies reviewed." Federal Judicial Center, *Reference Manual on Scientific Evidence* at 380 (2d ed. 2000).

applied to *all* patients and differed only slightly from the version of that warning that was in effect when Dr. Rasefske prescribed Effexor for Randy Aaron in July 2005. (*Id.*)

In September 2004, the FDA's researchers at Columbia released the results of their analysis of the 24 relevant pediatric clinical trials, which showed no actual suicides but a "modestly increased" odds ratio of 1.95 for suicidal acts and suicidal thinking in pediatric patients. (SUMF ¶ 54.) On October 15, 2004, the FDA issued a Public Health Advisory announcing that it would, among other things, require a "black box" warning for pediatric patients.[15] (SUMF ¶ 55.) The FDA-mandated pediatric "black box" warning was added to the labeling in January 2005, along with a modified version of the "Clinical Worsening and Suicide Risk" warning that, as it had since April 2004, applied to adult and pediatric patients. (SUMF ¶ 56.) This was the warning as of July 2005 when Dr. Rasefske prescribed Effexor for Aaron.

After the FDA finished analyzing the pediatric clinical trial data, it directed the manufacturers to submit their adult clinical trial data, a much larger universe that included 372 clinical trials involving nearly 100,000 patients. (SUMF ¶ 59.) As with the pediatric clinical trial data, only the FDA could analyze the adult data because only the FDA had access to all manufacturers' proprietary data. On June 30, 2005, the FDA issued a Public Health Advisory that "highlight[ed]," "*consistent with . . . the approved labeling*," the need for "[a]dults being treated with antidepressant medications, particularly those being treated for depression, [to] be watched closely for worsening of depression and for increased suicidal thinking or behavior." (SUMF ¶ 60 (italics added).) In November 2006, the FDA released the results of its analysis of the adult data, which showed an elevated risk of suicidality in patients under age 25, but no increased risk in patients 25 and older – the age group that included Randy Aaron. (SUMF ¶ 61.)

[15] As noted in footnote 2, "black box" warnings address "[s]pecial problems, particularly those that may lead to death or serious injury." 21 C.F.R. § 201.57(e) (Apr. 21, 2006).

Based on this analysis, the FDA modified the class-wide "black box" warning to include young adults under age 25, but also to report no "increase in the risk of suicidality with antidepressants . . . in adults beyond age 24." (SUMF ¶ 62.) The May 2007 suicide-related warnings remain in use today.

3. This Plaintiff's Claim Presents A Direct Conflict With Federal Law And, Therefore, Is Preempted.

The FDA's regulation of modern antidepressants' suicide-related warnings was unlike what *Levine* found the FDA's regulation of Phenergan's mode-of-administration warnings to have been. *Levine* noted that the FDA took 17 years to approve Phenergan's labeling and said that, when the FDA acted, the FDA did little that directly related to the relevant warnings. Here, the FDA exercised exclusive control over modern antidepressants' suicide-related warnings for two decades. After initially requiring a class-wide suicide precaution in the labeling, the FDA mandated its own detailed suicide-related warnings for all modern antidepressants in April 2004. In January 2005, months before Randy Aaron's Effexor prescription, the FDA revised its class-wide warnings to include a "black box" warning – the most prominent warning available. In June 2005, only weeks before Randy Aaron's Effexor prescription, the FDA reaffirmed the January 2005 warnings in a Public Health Advisory. And in May 2007, the FDA again revised its class-wide suicide-related warnings.

Levine said that the record there lacked "clear evidence that the FDA would not have approved a change to Phenergan's label." 129 S. Ct. at 1198. Here that "clear evidence" exists; namely, the FDA (1) drafted its own warnings, (2) required the entire class of modern antidepressants to carry those warnings, and (3) repeatedly rejected efforts to implement different or additional warnings. In the 1990s, the FDA rejected three citizen petitions seeking to modify the warnings. In September 2002, the FDA said in an *amicus curiae* brief that, as of that

date, it would have deemed additional suicide-related warnings to be misbranding in violation of federal law. When Wyeth proposed additional suicide-related information for Effexor's labeling in 2002 and added such information in 2003, the FDA directed Wyeth first not to include and then to remove that language.

Indeed, in its May 13, 2004 letter that told Wyeth to remove Effexor-specific suicide-related from Effexor's labeling, the FDA flatly said: "[T]he [FDA's] currently proposed language for **WARNINGS** is intended to *comprehensively address* this complex issue and [the FDA's] current understanding of the available data." (SUMF ¶ 49 (italics added) (bold in original).) And, if the claim here is that Wyeth should have warned of an increased risk of suicidality in adults like Randy Aaron, that would squarely conflict with (1) the FDA's warning in effect in July 2005, which said it was "*unknown* whether the suicidality risk" seen in pediatric patients "extends to adults" (SUMF ¶ 57 (italics added)); and (2) the current warning, which reports no increased risk in adults over age 24. (SUMF ¶ 62.) As the Seventh Circuit observed recently, "the Effexor warnings after 2002 actually more directly *disclaimed* any increased risk of suicidality in adults," and "[t]he 2007 black box warning . . . made explicit that for" persons over age 24, "no increased risk of suicidality ha[s] been shown." *Giles v. Wyeth*, 556 F.3d 596, 601 (7th Cir. 2009) (italics added).

In *Levine*, the Court's opinion reflects no FDA role in developing or analyzing the science relating to the risks of intra-arterial injection of Phenergan when treating nausea. Here, FDA scientists and FDA scientific advisory committees have, for decades, analyzed and reanalyzed data relating to suicidality and modern antidepressants, which are used daily by tens of millions of patients and, in some instances, are household names (*e.g.*, the book *Prozac Nation – Young and Depressed In America: A Memoir* (1994) that was made into the movie "Prozac

Nation" (2001)). Until mid-2003, the FDA had identified no increased risk. Beginning in 2003, the FDA commissioned its own scientific reanalyses of pediatric and then adult clinical trial data and, as the science developed, the FDA promptly alerted health care providers of new scientific results and conclusions through Public Health Advisories and revised class-wide warnings.

The drug at issue in *Levine*, Phenergan, was "corrosive" when injected into an artery, and, according to the Court, "as amputations continued to occur, [the defendant] could have analyzed the accumulating data and added a stronger warning about IV-push administration." 129 S. Ct. at 1191, 1197. Here, determining whether modern antidepressants contribute to suicide or suicidality was (and is) extremely difficult. Suicide and suicidality are rare events that are difficult to assess in one manufacturer's clinical trials that involve, at most, a few thousand patients. And antidepressants treat depression – the strongest single risk factor for suicide and suicidality – making it difficult to distinguish between depression-induced and drug-induced suicidality. Accordingly, a single manufacturer's clinical trial data generally was insufficient to form scientific conclusions on that topic. Instead, scientific conclusions about antidepressants and suicidality, when possible at all, were based on analyses of industry-wide clinical trial data – proprietary data that was available only to the FDA in its role as regulator.

In *Levine*, the Court said there was "newly acquired information" that, in the Court's view, allowed adding a CBE warning. *Levine*, 129 S. Ct. at 1197. Here, plaintiff has identified no "newly acquired information" that would have allowed Wyeth to make a CBE modification to Effexor's suicide-related warnings in July 2005, which is not surprising because the FDA's warnings were just six months old and had been reiterated by the FDA in a late June 2005 Public Health Advisory. Thus, it would have been impossible for Wyeth to provide the warnings plaintiff asserts should have been provided and simultaneously to comply with federal law.

The warnings at issue in *Levine* related to one of several modes of administering a nausea drug; thus, while excessive warnings might deter physicians from using the faster IV-push method when circumstances warranted, patients still could receive the drug. Here, over-deterrence through over-warning would prevent patients from taking antidepressants to treat their depression – a debilitating, and potentially fatal, condition. As the FDA explained in its *Motus amicus* brief, "[u]nderutilization of a drug based on dissemination of scientifically unsubstantiated warnings" could "deprive patients of beneficial, possibly lifesaving treatment." (SUMF ¶ 63.) These concerns were well-founded. Suicide rates fell dramatically after the introduction of modern antidepressants in the late 1980s. (SUMF ¶ 64.) Since the FDA began modifying antidepressant warnings in 2004, studies have shown reduced diagnoses of depression, reduced antidepressant use, and possible increased suicide rates. (SUMF ¶ 65.)

Levine recognized that in some circumstances the Court would "conclude that it was impossible for [the prescription drug manufacturer] to comply with both federal and state requirements," just as the Court "recognize[d] that some state-law claims might well frustrate the achievement of congressional objectives." 129 S. Ct. at 1198, 1204. This is that case.

C. Plaintiff Cannot Provide Summary Judgment Evidence To Support An Essential Element Of His Design Defect And Express Warranty Claims.

Under Pennsylvania law, determining "whether a product was negligently designed turns on whether an alternative, feasible, safer design would have lessened or eliminated the injury plaintiff suffered." *Berrier v. Simplicity Mfg., Inc.*, 563 F.3d 38, 64 (3d Cir. 2009) (quotation marks, italics, and citation omitted). To pursue an express warranty claim, a plaintiff "must demonstrate that [the defendant] made an actual affirmation of fact or promise that constitute[d] a warranty . . . that formed the 'basis of the bargain.'" *Jeter v. Brown & Williamson Tobacco*

Corp., 294 F. Supp. 2d 681, 686 (W.D. Pa. 2003) (Schwab, J.) (*citing* Pa. Cons. Stat. Ann. § 2313), *aff'd*, 113 Fed. Appx. 465 (3d Cir. 2004).

Here, plaintiff cannot provide summary judgment evidence showing "an alternative, feasible, safer design" for Effexor that would have somehow prevented Randy Aaron's suicide. Similarly, plaintiff has no summary judgment evidence to "demonstrate that [Wyeth] made an actual affirmation of fact or promise that constitute[d] a warranty" that patients taking Effexor would not commit suicide. "[T]he plain language of Rule 56(c) mandates the entry of summary judgment . . . against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 325 (1986). Given plaintiff's inability to establish an essential element of his negligent design and express warranty claims, "Rule 56(c) mandates the entry of summary judgment" dismissing those claims.

III. CONCLUSION

The Court should grant Wyeth summary judgment and dismiss plaintiff's complaint.

Respectfully submitted,

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/s/ James M. Jones

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CERTIFICATE OF SERVICE

I hereby certify that a true and accurate copy of the foregoing Memorandum in Support of Defendant Wyeth's Motion for Summary Judgment was served via the district court's electronic filing system, this 23rd day of June, 2009, upon the following:

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